AMENDMENTS TO THE SPECIFICATION

Please delete the paragraph inserted on March 24, 2006 at page 15, line 15 and ending on page 17, line 4 (page and line numbers are for the application as filed) and replace it with the following, which is identical to that deleted on March 24, 2006:

Said advantages include but are not limited to the use of binding agents that are directed specifically against the fragments of interest and not portions of the thrombospondin molecule outside of these fragments, the use of relevant peptides and/or thrombospondin fragments to generate said binding agents (such as antibodies), the use of relevant peptides and/or thrombospondin fragments as assay calibrators, and the use of relevant peptides and/or thrombospondin fragments as assay indicators.

Any of several acceptable approaches can be used for the assay of a thrombospondin fragment (or fragments) wherein the assay distinguishes it from thrombospondin, and more than one of these can be used in a given assay. In one approach, the assay comprises a step wherein the fragment is physically separated from the thrombospondin. Generally that approach is combined with a step in which the presence of the fragment or thrombospondin is shown by their reaction with a specific binding agent. In particular embodiments, the physical separation technique is selected from the group consisting of gel electrophoresis, dialysis, chromatography, size chromatography, affinity chromatography, immunoaffinity chromatography, adsorption, immunoadsorption, isoelectric focusing, mass spectrometry, centrifugation, sedimentation, floatation, precipitation, immunoprecipitation, and gel filtration.

In a second approach, the assay distinguishes the fragment (or fragments) based on one or more epitopes (here "epitope" meaning a target to which a binding agent, *i.e.,* an antibody or a non-antibody, binds) in the fragment that are not present in thrombospondin, including but not limited to an epitope at an end of a fragment and an epitope that is displayed by a fragment but is shielded in thrombospondin.

In a third approach, the assay distinguishes the fragment (or fragments) based on one or more epitopes in thrombospondin that are not present in the fragment. As an illustrative but not

restrictive example, an epitope shared by thrombospondin and a thrombospondin fragment is used to obtain a quantitation of a total, thrombospondin plus thrombospondin fragment(s), from which is then subtracted a quantitation of thrombospondin obtained using an epitope present in thrombospondin but not present in a fragment. The difference between the two quantitations is a quantitation of the amount of fragment. As an example, epitopes in thrombospondin but not in at least one fragment from the group of an 80 to 100 kDa, a 40 to 55 kDa, or a 20 to 35 kDa fragment present in plasma can be selected from the group consisting of an epitope from outside the protease-resistant central core domain, an epitope in the N-terminal domain, an epitope in the N-terminal heparin-binding domain, a heparin-binding sequence in the N-terminal domain, a heparin-binding sequence in the N-terminal domain selected from the group consisting of residues 23-32 (RKGSGRRLVK), residues 23-29 (RKGSGRR), and residues 77-83 (RQMKKTR) of the mature protein (see Chapter 2, "The primary structure of the thrombospondins" in The Thrombospondin Gene Family by JC Adams, RP Tucker, & J Lawler, Springer-Verlag: New York, 1995, pp. 11-42, but especially p. 13 & Table 2.1; Chapter 6, "Mechanistic and functional aspects of the interactions of thrombospondins with cell surfaces," *ibidem* pp. 105-157, but especially pp. 108 & 114; Lawler J et al. Expression and mutagenesis of thrombospondin. Biochemistry. 1992 Feb 4;31(4):1173-80; and Cardin AD & Weintraub HJ. Molecular modeling of protein-glycosaminoglycan interactions. Arteriosclerosis. 1989 Jan-Feb;9(1):21-32), a heparin-binding sequence in the N-terminal domain selected from the group consisting of residues 22-29 (ARKGSGRR), residues 79-84 (MKKTRG), and residues 178-189 (RLRIAKGGVNDN) of the mature protein (reviewed in the Discussion section of Voland C et al.: Platelet-osteosarcoma cell interaction is mediated through a specific fibrinogen-binding sequence located within the N-terminal domain of thrombospondin 1. J Bone Miner Res. 2000 Feb;15(2):361-368), an epitope in the C-terminal domain, an epitope in the C-terminal cell-binding domain, a thrombospondin epitope not found in a plasma fragment, a thrombospondin epitope not found in a plasma fragment of 80 to 100 kDa, a thrombospondin epitope not found in a plasma fragment of 40 to 55 kDa, and a thrombospondin epitope not found in a plasma fragment of 20 to 35 kDa, where all kDa molecular weights are those after reduction. It is understood that the absence of a strong, functional heparin-binding domain from a

thrombospondin fragment in plasma will be a factor allowing its accumulation in plasma (many heparin- or heparan-binding proteins are cleared from plasma very quickly;

Please delete the paragraph inserted on March 24, 2006 at page 25, line 6 and ending on page 25, line 20 (page and line numbers are for the application as filed) and replace it with the following, which is identical to that deleted on March 24, 2006:

coli inclusion bodies, Protein Expr Purif. 2002 Nov; 26(2):301-308.)

Non-antibodies also include aptamers and non-antibodies that comprise aptamers. Aptamers are DNA or RNA molecules that have been selected (*e.g.,* from random pools) on the basis of their ability to bind to another molecule (discussed for example at the web site of the Ellington lab, in the Institute of Cellular and Molecular Biology, at the University of Texas at Austin, http://aptamer.icmb.utexas.edu/), wherein said molecule can be a nucleic acid, a small organic compound, or a protein, peptide, or modified peptide (such as thrombospondin or a portion thereof.). An aptamer beacon is an example of a non-antibody that comprises an aptamer (See Hamaguchi N et al., Aptamer beacons for the direct detection of proteins. Anal. Biochem. 2001 Jul 15;294(2):126-131.)

Angiocidin is a CSVTCG-specific tumor cell adhesion receptor, see patent application WO 0105968, also NCBI protein accession number CAC32386.1 and/or CAC32387.1 (corresponding to nucleotide accession numbers AX077201 and AX077202), the amino acid sequences specified by those two protein accession numbers as of the date of filing of this application being incorporated herein by reference. It is understood that anti-

Please delete the paragraph inserted on March 24, 2006 at page 32, line 8 and ending on page 32, line 16 (page and line numbers are for the application as filed) and

replace it with the following, which is identical to that deleted on March 24, 2006:

has been purified (for example has been isolated from gels on which the plasma has been electrophoresed). A purified fragment is not one that is in human plasma, or other part of a human, and that has not undergone at least some degree of purification.

A "synthesized fragment" is, for example, one that has been synthesized in a laboratory (*e.g.,* by recombinant DNA technology or by chemical synthesis) so as to have the primary structure of such a fragment or a portion thereof.

The amino acid sequence of human thrombospondin-1 from GenBank is:

ACCESSION NM_003246 (protein_id=NP_003237.1)

VERSION NM_003246.1 GI:4507484

Please delete the paragraph inserted on March 24, 2006 at page 44, line 9 and ending on page 45, line 11 (page and line numbers are for the application as filed) and replace it with the following, which is identical to that deleted on March 24, 2006:

~50-kDa fragment but not the ~30-kDa fragment (this is followed by a numerical calculation to yield the amounts of ~85-kDa fragment and of ~50-kDa fragment separately). An example of this use of color-coded beads can be found at http://www.lincoresearch.com/lincoplex/technology.htm, the web site for Linco Research, Inc.

Another option for analyzing multiple analytes is SearchLight™ Proteome Arrays, which are multiplexed sandwich ELISAs, currently adapted for the quantitative measurement of two to 16 proteins per well. It is understood herein that the method can also be used for protein fragments, such as one or more thrombospondin fragments. Using a spotting technique, 2 to 16 target-specific antibodies are bound to each well of a microplate, although it is understood that this number can be expanded with improved spotting techniques and/or larger wells. Following a standard sandwich ELISA procedure, luminescent signals are imaged with a cooled CCD (charged coupled device) camera. The image is then analyzed using Array Vision™ software.

The amount of signal generated at each spot is related to the amount of target protein in the original standard or sample. Values for specific proteins and/or protein fragments can be calculated based on the position of the spots and comparison of density values for unknowns to density values for known standards (and TSP fragments or peptides can be used as standards). The SearchLight™ technology is available through Pierce Boston Technology Center (http://www.searchlightonline.com/), including customized arrays using proprietary reagents from outside Pierce or assay targets not currently available at Pierce (see http://www.searchlightonline.com/custom_array.cfm).

Other assay methods are also contemplated. They include but are not limited to immunoblotting, dot-blotting and immunoturbidimetric assays (for a detailed example of this last approach with another plasma protein, see Levine, D.M. and Williams, K.J.: Automated measurement of mouse apolipoprotein B: convenient screening tool for mouse models of atherosclerosis. *Clin. Chem.* 43:669-674, 1997), as well as blotting and/or turbidimetric assays that use binding agents in general. Other competitive assays are also contemplated, such as ones in which material in a standard and an unknown competes with one or more labeled peptides, one or more labeled TSP fragments, and/or labeled TSP for binding to an agent that binds TSf, such as an anti-TSf antibody (the label is then used for detection and hence quantification). One example of this approach is to immobilize an anti-TSf antibody, and then add sample mixed with labeled peptide, labeled TSP fragments, or labeled TSP, so that sample and labeled material compete for binding to the immobilized antibody (note that this approach requires only one anti-TSf antibody). Binding of labeled material is then

Once all the above amendments have been done, please proceed as follows:

Please replace the paragraph beginning on page 16, line 4 and ending on page 17 line 6 with the following rewritten paragraph:

In a third approach, the assay distinguishes the fragment (or fragments) based on one or more epitopes in thrombospondin that are not present in the fragment. As an illustrative but not restrictive example, an epitope shared by thrombospondin and a thrombospondin fragment is used to obtain a quantitation of a total, thrombospondin plus thrombospondin fragment(s), from which is then subtracted a quantitation of thrombospondin obtained using an epitope present in thrombospondin but not present in a fragment. The difference between the two quantitations is a quantitation of the amount of fragment. As an example, epitopes in thrombospondin but not in at least one fragment from the group of an 80 to 100 kDa, a 40 to 55 kDa, or a 20 to 35 kDa fragment present in plasma can be selected from the group consisting of an epitope from outside the protease-resistant central core domain, an epitope in the N-terminal domain, an epitope in the N-terminal heparin-binding domain, a heparin-binding sequence in the N-terminal domain, a heparin-binding sequence in the N-terminal domain selected from the group consisting of residues 23-32 (RKGSGRRLVK SEQ ID NO:59), residues 23-29 (RKGSGRR SEQ ID NO:60), and residues 77-83 (RQMKKTR SEQ ID NO:61) of the mature protein (see Chapter 2, "The primary structure of the thrombospondins" in The Thrombospondin Gene Family by JC Adams, RP Tucker, & J Lawler, Springer-Verlag: New York, 1995, pp. 11-42, but especially p. 13 & Table 2.1; Chapter 6, "Mechanistic and functional aspects of the interactions of thrombospondins with cell surfaces," *ibidem* pp. 105-157, but especially pp. 108 & 114; Lawler J et al. Expression and mutagenesis of thrombospondin. Biochemistry. 1992 Feb 4;31(4):1173-80; and Cardin AD & Weintraub HJ. Molecular modeling of protein-glycosaminoglycan interactions. Arteriosclerosis. 1989 Jan-Feb;9(1):21-32), a heparin-binding sequence in the N-terminal domain selected from the group consisting of residues 22-29 (ARKGSGRR SEQ ID NO:62), residues 79-84 (MKKTRG SEQ ID NO:63), and residues 178-189 (RLRIAKGGVNDN SEQ ID NO:64) of the mature protein (reviewed in the Discussion section of Voland C et al.: Platelet-osteosarcoma cell interaction is mediated through a specific fibrinogen-binding sequence located within the N-terminal domain of thrombospondin 1. J Bone Miner Res. 2000 Feb;15(2):361-368), an epitope in the C-terminal domain, an epitope in the C-terminal cell-binding domain, a

thrombospondin epitope not found in a plasma fragment, a thrombospondin epitope not found in a plasma fragment of 80 to 100 kDa, a thrombospondin epitope not found in a plasma fragment of 40 to 55 kDa, and a thrombospondin epitope not found in a plasma fragment of 20 to 35 kDa, where all kDa molecular weights are those after reduction. It is understood that the absence of a strong, functional heparin-binding domain from a thrombospondin fragment in plasma will be a factor allowing its accumulation in plasma (many heparin- or heparan-binding proteins are cleared from plasma very quickly; see for example, Wallinder L et al. Rapid removal to the liver of intravenously injected lipoprotein lipase. Biochim Biophys Acta. 1979 Oct 26;575(1):166-73).

Please replace the paragraph beginning on page 23, line 3 and ending on page 23 line 17 with the following rewritten paragraph:

Raising conventional antibodies (also referred to herein simply as "antibodies" as opposed to "single chain antibodies"; and an example of a conventional antibody is IgG, which is composed of two heavy chains and two light chains) is merely one of a number of methods that are generally based on the approach of random, semi-random, directed, combinatorial, and/or other means for the generation of large numbers of diverse peptides and/or non-peptides, that is then followed by a selection procedure to identify within this large number those peptides and/or non-peptides that bind to a target and/or an epitope within a target. Selection can then be followed by methods for improving the peptides and/or non-peptides to achieve better affinity and/or specificity. These diverse peptides and/or non-peptides may be conventional multi-chain antibodies (polyclonal or monoclonal), single-chain antibodies, or non-antibodies, including but not limited to peptides, products of phage display, aptamers, DNA, RNA, or modified DNA or

RNA. Also contemplated are thrombospondin receptors and/or binding proteins (such as a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, CD36, angiocidin, 26S proteasome non-ATPase regulatory subunit 4, and/or anti-secretory factor).

Please replace the paragraph beginning on page 28, line 1 and ending on page 28 line 9 with the following rewritten paragraph:

Such kits wherein said protein non-antibody is selected from the group consisting of a thrombospondin receptor, a thrombospondin receptor that binds within a protease-resistant core region, a thrombospondin receptor that binds a TSP fragment present in the plasma of a cancer patient, a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, a CD36 (which reportedly binds CSVTCG (SEQ ID NO:54); see Carron JA et al., A CD36-binding peptide from thrombospondin-1 can stimulate resorption by osteoclasts in vitro. Biochem Biophys Res Commun. 2000 Apr 21;270(3):1124-7), angiocidin, anti-secretory factor, 26S proteasome non-ATPase regulatory subunit 4, fragments thereof that bind to their respective targets, and combinations, chimeras, and recombinant versions of said receptors and fragments.

Please replace the paragraph beginning on page 36, line 9 and ending on page 37 line 22 with the following rewritten paragraph:

It is believed that the ~85 kDa, ~50 kDa, and ~30 kDa fragments all contain an immunogenic portion of "collagen type V-binding domain" of thrombospondin. In a preferred aspect of the invention, the fragments are detected by antibody that binds to such a domain, as is believed to be the case for the TSP Ab-4 monoclonal antibody referred to below. Because the collagen V-binding domain is relatively small (~19 kDa; see Takagi *et al.* JBC 1993), it is concluded from the apparent molecular weights of these fragments, which are substantially greater than 19kDa, that additional portions of the thrombospondin molecule must also be

present in these fragments (multimers of the 19-kDa region are not a plausible explanation for the higher molecular weights, because the 19-kDa region does not comprise the region of inter-chain disulfide bonds, plus the fact that the gels in Figures 3 and 4 were run under reducing conditions). It is believed that additional portions come from the protease-resistant central core domain of thrombospondin, which can be selected from the group of thrombospondin domains consisting of the region of inter-chain disulfide bonds, the procollagen-like domain, a type 1 repeat, and to some extent a type 2 repeat and a type 3 repeat (see Prater CA *et al.* The properdin-like type 1 repeats of human thrombospondin contain a cell attachment site. J Cell Biol. 1991 Mar;112(5):1031-40; Schultz-Cherry S *et al.* The type 1 repeats of thrombospondin 1 activate latent transforming growth factor-beta. J Biol Chem. 1994 Oct 28;269(43):26783-8; Figure 6.2 in Adams JC et al. The Thrombospondin Gene Family, 1995, p. 107; and chymotryptic and tryptic fragments of thrombospondin indicated schematically in Figure 1 of this application). See also the sequence ranges given earlier in this Application. Note that several aforementioned peptides, such as, CNSPSPQMNGKPCEGEAR (SEQ ID NO:8) (residues 444-461), RKVTEENKELANELRPP (SEQ ID NO:9) residues 281-297); PQMNGKPCEGEAR (SEQ ID NO:11) (residues 449-461); CEGEAR (SEQ ID NO:12) ~~(residues 456-461~~ (residues 456-461); and RKVTEENKE (SEQ ID NO:13) (residues 281-289) are within the protease-resistant central core domain. An antibody against a region outside of a collagen V-binding domain, but present in a thrombospondin fragment present in a cancer patient, is also preferred.

Replace the text added after page 50, line 6 by Amendment on October 31, 2006, with the following paragraphs:

--The current inventions may be further summarized and numbered in the following fashion (using 164 numbered Paragraphs) analogous to the procedure for numbering claims, where the word "Paragraph has been substituted for the word "Claim":

1. A purified thrombospondin fragment that has been extracted from a bodily fluid, said fragment being one within a molecular weight range selected from the group consisting of 80 to 110 kDA, 40 to 60 kDa, and 20 to 35 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

2. A purified thrombospondin fragment of Paragraph 1, wherein the bodily fluid is blood plasma.

3. A purified thrombospondin fragment of Paragraph 1, wherein the fragment's molecular weight is one within a molecular weight range selected from the group consisting 85 to 90 kDa fragment, 47 to 53 kDa, and 27 to 33 kDa.

4. A molecule identical in primary structure to the compound of Paragraph 2.

5. A fragment of Paragraph 4 further modified to have a modification selected from the group consisting of glycosylation, deglycosylation, β-hydroxylation, alkylation, reduction, denaturation, renaturation, calcium depletion, calcium supplementation, conjugation, and addition of groups or moieties to aid conjugation, stability, and/or immunogenicity.

6. A purified and/or synthetic thrombospondin fragment or portion thereof, said fragment selected from the group comprising one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues K-412 and I-530, inclusive;

one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues I-530 and R-733, inclusive;

and one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues R-792 and Y-982, inclusive, said portion being at least 4 amino acyl acids in length.

7. A purified and/or synthetic thrombospondin fragment or portion thereof, selected from the group comprising one that starts between amino acyl residues N-230 and G-253 inclusive, and ends between amino acyl residues V-400 and S-428, inclusive;

one that starts between amino acyl residues N-230 and G-253, inclusive, and ends between amino acyl residues D-527 and S-551, inclusive;

and one that starts between amino acyl residues N-230 and G-253, inclusive, and ends between amino acyl residues G-787 and V-811, inclusive, said portion being at least 4 amino

acyl acids in length.

8. A purified thrombospondin fragment, the molecular weight of said fragment not exceeding 100 kDa, said fragment comprising at least 4 contiguous amino acyl residues from the thrombospondin sequence, wherein the amino acid sequence of the fragment is limited to the group consisting of a fragment that is outside of a thrombospondin region defined in paragraph 6 and a fragment that is outside of a thrombospondin region defined in paragraph 7.

9. A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises a domain or a part thereof within the protease-resistant core of thrombospondin, said domain being selected from the group consisting of a domain of inter-chain disulfide bonds, an oligomerization domain, a procollagen-like domain, a type 1 repeat, a type 2 repeat, and a type 3 repeat.

10. A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises an amino acid sequence selected from the group consisting of TEENKE (SEQ ID NO: 1), CLQDSIRKVTEENKE (SEQ ID NO: 2), LQDSIRKVTEENKE (SEQ ID NO: 3), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEARE (SEQ ID NO: 5), EDTDLD (SEQ ID NO: 6), YAGNGIICGEDTDLD (SEQ ID NO: 7), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), RKVTEENKELANELRRP (SEQ ID NO: 9), CRKVTEENKELANELRRP (SEQ ID NO: 10), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), RKVTEENKE (SEQ ID NO: 13), TERDDD (SEQ ID NO: 24), DFSGTFFINTERDDD (SEQ ID NO: 25), ERKDHS (SEQ ID NO: 26), TRGTLLALERKDHS (SEQ ID NO: 27), CTRGTLLALERKDHS (SEQ ID NO: 28), DDKFQD (SEQ ID NO: 29), ANLIPPVPDDKFQD (SEQ ID NO: 30), CANLIPPVPDDKFQD (SEQ ID NO: 31), DCEKME (SEQ ID NO: 32), EDRAQLYIDCEKMEN (SEQ ID NO: 33), CGTNRIPESGGDNSVFD (SEQ ID NO: 34), NRIPESGGDNSVFD (SEQ ID NO: 35), GWKDFTAYRWRLSHRPKTG (SEQ ID NO: 36), CGWKDFTAYRWRLSHRPKTG (SEQ ID NO: 37), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18),

EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion of such an amino acid sequence.

11. A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises a portion of a collagen type V binding domain.

12. A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment comprises an epitope for binding the TSP Ab-4 antibody.

13. A purified and/or synthetic thrombospondin fragment, the molecular weight of said fragment not exceeding 110 kDa, said fragment being at least 4 contiguous amino acyl residues in length, and wherein the fragment does not comprise a fibrinogen-binding region selected from the group consisting of (1) a fibrinogen-binding domain within a 210-kDa fragment of TSP, where said 210-kDa fragment is composed of three 70-kDa fragments that contain the region of interchain disulfide bonds, the procollagen homology region, and the type 1 and type 2 repeats, (2) a fibrinogen-binding region in the amino-terminal domain of thrombospondin, (3) a fibrinogen-binding region in an 18-kDa amino-terminal heparin-binding domain of thrombospondin, and (4) a region corresponding to synthetic peptide N12/I encompassing amino acid residues 151-164 (I-151 to P-164) of the N-terminal domain of thrombospondin-1.

14. A fragment of Paragraphs 6,7, 8, 9,10,11,12 or 13, said fragment being at least 6 contiguous amino acyl residues in length.

15. A fragment of Paragraphs 6,7,8,9,10,11,12 or 13, wherein the molecular weight of the fragment does not exceed 55 kDa.

16. A fragment of Paragraphs 5 6,7,8,9,10,11,12 or 13, wherein the molecular weight of the fragment does not exceed 35 kDa.

17. A fragment or portion thereof specified in Paragraphs 6,7,8, 9,10,11,12 or 13, said fragment or portion comprising at least 13 contiguous amino acyl residues.

18. A fragment or portion thereof specified in Paragraphs 6,7,8, 9,10,11,12 or 13, said

fragment or portion being a synthetic peptide, said peptide being either glycosylated or nonglycosylated, and/or either ß-hydroxylated or not ß-hydroxylated.

19. A thrombospondin fragment or portion thereof specified in Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 that comprises a detectable label, said label being either intrinsic or an added moiety.

20. A thrombospondin fragment or portion thereof specified in Paragraph 1, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein said fragment or portion comprises a detectable label that is selected from the group consisting of a radioactive label, a fluorescent label, a chemical label, a colorometric label, an enzymatic label, a non-fluorescent label, a non-radioactive label, a biotin moiety, and an avidin moiety.

21. A method to detect and/or quantify a thrombospondin fragment of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Paragraph 6 or 7.

22. A method of paragraph 21, wherein the method distinguishes the thrombospondin fragment or fragment portion from thrombospondin.

23. A method of Paragraph 22 wherein the method comprises a step wherein the fragment or fragment portion is physically separated from the thrombospondin.

24. A method of Paragraph 23 wherein the physical separation is accomplished using a technique that is selected from the group consisting of gel electrophoresis, dialysis, chromatography, size chromatography, affinity chromatography, immunoaffinity chromatography, adsorption, immunoadsorption, isoelectric focusing, mass spectrometry, centrifugation, sedimentation, floatation, precipitation, immunoprecipitation, and gel filtration.

25. A method of Paragraph 22 that distinguishes the fragment or fragment portion based on one or more epitopes in the fragment or fragment portion that are not present in thrombospondin.

26. A method of Paragraph 22 that distinguishes the fragment or fragment portion based on one or more epitopes in thrombospondin that are not present in the fragments, said method comprising the steps of:

1) utilizing an epitope shared by thrombospondin and the thrombospondin fragment or thrombospondin portion as a target for a binding molecule, such as an antibody, to obtain a

quantitation of a total, thrombospondin plus either the thrombospondin fragment or thrombospondin portion,

2) utilizing an epitope present in thrombospondin but not present in the fragment or thrombospondin portion to obtain a quantitation of thrombospondin only; and

3) utilizing the difference between the quantitations obtained in steps (1) and (2) as a quantitation of the amount of fragment or thrombospondin portion.

27. The method of Paragraph 26 wherein in Step 1 the epitope is contained within an amino acid sequence selected from the group consisting of a fragment of paragraph 6, a fragment of paragraph 7, a fragment of paragraph 9, a fragment of paragraph 11, a fragment of paragraph 12, TEENKE (SEQ ID NO: 1), CLQDSIRKVTEENKE (SEQ ID NO: 2), LQDSIRKVTEENKE (SEQ ID NO: 3), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEARE (SEQ ID NO: 5), EDTDLD (SEQ ID NO: 6), YAGNGIICGEDTDLD (SEQ ID NO: 7), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), RKVTEENKELANELRRP (SEQ ID NO: 9), CRKVTEENKELANELRRP (SEQ ID NO: 10), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), RKVTEENKE (SEQ ID NO: 13), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion, at least 3 amino acyl residues in length of such an amino acid sequence.

28. The method of Paragraph 26 wherein in Step 2 the epitope is contained within an amino acid sequence selected from the group consisting of a fragment of paragraph 8, TERDDD (SEQ ID NO: 24), DFSGTFFINTERDDD (SEQ ID NO: 25), ERKDHS (SEQ ID NO: 26), TRGTLLALERKDHS (SEQ ID NO: 27), (C)TRGTLLALERKDHS (SEQ ID NO: 28), DDKFQD (SEQ ID NO: 29), ANLIPPVPDDKFQD (SEQ ID NO: 30), (C)ANLIPPVPDDKFQD (SEQ ID NO: 31), DCEKME (SEQ ID NO: 32), EDRAQLYIDCEKMEN (SEQ ID NO: 33), CGTNRIPESGGDNSVFD (SEQ ID NO: 34), NRIPESGGDNSVFD (SEQ ID NO: 35), GWKDFTAYRWRLSHRPKTG (SEQ ID NO: 36),

CGWKDFTAYRWRLSHRPKTG (SEQ ID NO: 37), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), YAGNGIICGEDTDLD (SEQ ID NO: 7), EDTDLD (SEQ ID NO: 6), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), PQMNGKPCEGEARE (SEQ ID NO: 5), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion, at least 3 amino acyl residues in length of such an amino acid sequence, provided that said peptide with a designated SEQ ID NO. does not comprise an epitope used in step 1

29. A method of Paragraph 21 wherein the method is applied to a sample of material taken or gathered from an organism.

30. A method of Paragraph 21 wherein the organism is a human.

31. A method of Paragraph 21 wherein the organism is a nonhuman.

32. A method of Paragraph 21 wherein the method is applied to a sample of human plasma.

33. A method of Paragraph 21 wherein the method is performed in order to detect the presence of, or monitors the course of, a disease or condition.

34. A method of Paragraph 33 wherein the disease or condition is selected from the group consisting of a cancer, renal failure, renal disease, atopic dermatitis, vasculitis, acute vasculitis, renal allograft, asthma, diabetes mellitus, myocardial infarction, liver disease, splenectomy, dermatomyositis, polyarteritis nodosa, systemic lupus erythematosus, lupus erythematosus, Kawasaki syndrome, non-specific vasculitis, juvenile rheumatoid arthritis, rheumatoid arthritis, vasculitis syndrome, Henoch-Schönlein purpura, thrombocytopenic purpura, purpura, an inflammatory condition, a condition associated with clotting, a condition associated with platelet activation, a condition associated with intravascular platelet activation, a condition associated with consumption of platelets, heparin-induced thrombocytopenia, disseminated intravascular coagulation, intravascular coagulation, extravascular coagulation, a condition associated with

endothelial activation, a condition associated with production and/or release of thrombospondin and/or a thrombospondin fragment, urticaria, hives, angioedema, a drug reaction, an antibiotic reaction, an aspartame reaction, atopic dermatitis, eczema, hypersensitivity, scleroderma, conditions associated with plugging of vessels, a condition associated with a cryofibrinogen, a condition associated with a cryoglobulin, and a condition associated with an anti-cardiolipin antibody.

35. A method of Paragraph 33 wherein the disease is a cancer.

36. A method of Paragraph 35 wherein the cancer is selected from the group consisting of an adenoma, adenocarcinoma, carcinoma, lymphoma, leukemia, solid cancer, liquid cancer, metastatic cancer, pre-metastatic cancer, non-metastatic cancer, a cancer with vascular invasion, internal cancer, skin cancer, cancer of the respiratory system, cancer of the circulatory system, cancer of the musculoskeletal system, cancer of a muscle, cancer of a bone, cancer of a joint, cancer of a tendor or ligament, cancer of the digestive system, cancer of the liver or biliary system, cancer of the pancreas, cancer of the head, cancer of the neck, cancer of the endocrine system, cancer of the reproductive system, cancer of the male reproductive system, cancer of the female reproductive system, cancer of the genitourinary system, cancer of a kidney, cancer of the urinary tract, cancer of a sensory system, cancer of the nervous system, cancer of a lymphoid organ, blood cancer, cancer of a gland, cancer of a mammary gland, cancer of a prostate gland, cancer of an endometrial tissue, cancer of a mesodermal tissue, cancer of an ectodermal tissue, cancer of an endodermal tissue, a teratoma, a poorly-differentiated cancer, a well-differentiated cancer, and a moderately differentiated cancer.

37. A method of Paragraph 21 wherein the method is performed to measure the degree of platelet activation.

38. A method of Paragraph 21 wherein the method is performed to measure the degree of secretion of thrombospondin and/or a thrombospondin fragment from a tissue.

39. A method of paragraph 38 wherein the tissue is selected from the group consisting of a cancer, a neoplasm, an activated endothelium, and a stroma.

40. A method of Paragraph 21 wherein the method is performed on plasma that was obtained by a method that prevents or reduces platelet activation and/or protease activity during

sample collection and/or storage.

41. A method of Paragraph 40 wherein the method does not comprise the use of a tournequet and/or stasis.

42. A method of Paragraph 40 wherein the method comprises a step selected from the group consisting of: (1) use of a large-bore needle, (2) discarding of the initial portion of the collected blood, (3) use of a coated needle, (4) use of a coated tubing, (5) storage of sample between -1°C and 5°C, and (6) separation of plasma from cellular components of blood within 30 minutes of sample collection.

43. A method of Paragraph 40 wherein the method comprises the use of an agent selected from the group consisting of a platelet inhibitor, a protease inhibitor, a serine protease inhibitor, an enzyme inhibitor, an inhibitor of an enzyme that is divalent cation dependent, a heparin, a heparin fragment, a low-molecular weight heparin, a heparan, a heparan sulfate, an anticoagulant, a COX inhibitor, an inhibitor of a cell-adhesion molecule, an inhibitor of a surface receptor, a glycoprotein inhibitor, an inhibitor of a glycoprotein IIb/IIIa receptor, a thrombin inhibitor, an inhibitor of degranulation, a chelator, a citrate compound, theophylline, adenosine, and dipyridamole.

44. A method of Paragraph 21 or paragraph 33, said method further comprising an method not based on a thrombospondin fragment or portion thereof.

45. A method of Paragraph 44 wherein the test not based on a thrombospondin fragment or portion thereof is selected from the group consisting of an imaging test, a radiographic test, a nuclear medicine test, a magnetic resonance imaging test, a blood test, a biopsy, a histologic test, a cytologic test, an immunohistologic test, a genetic test, a guaiac test, a test for fecal occult blood, a test for fecal blood, a test for fecal DNA, a test for a fecal cancer marker, a cancer test not based on a thrombospondin fragment or portion thereof, a receptor test, an estrogen receptor test, a disease test not based on a thrombospondin fragment or portion thereof, an endoscopy, an upper gastrointestinal endoscopy, a lower gastrointestinal endoscopy, a colonoscopy, a sigmoidoscopy, a gastroscopy, a laparoscopy, a laparatomy, a lymph node biopsy, a surgery, and a bronchoscopy.

46. A method of Paragraph 45 wherein the blood test is selected from the group

consisting of a cancer antigen test, a cancer gene test, a cancer DNA test, a cancer mRNA test, a cancer RNA test, a cancer protein test, a cancer glycoprotein test, a cancer carbohydrate test, a cancer lipid test, a prostate specific antigen test, a test of carcinoembryonic antigen, a test of cancer antigen CA-125, a test of alpha-fetoprotein, a test of CA15-3, a test of CA19-9, a test of malignin, a test of anti-malignin antibody, a test of anti-secretory factor, a cancer antigen that contains a carbohydrate epitope, a cancer antigen that contains a protein or polypeptide epitope, a cancer antigen that contains a lipid epitope, a cancer antigen that contains a mixed epitope, CA 27.29, and episialin.

47. A method of Paragraph 36, said method further comprising an method not based on a thrombospondin fragment or portion thereof.

48. A method of Paragraph 47, wherein the test not based on a thrombospondin fragment or portion thereof is selected from the group consisting of an imaging test, a radiographic test, a nuclear medicine test, a magnetic resonance imaging test, a blood test, a biopsy, a histologic test, a cytologic test, an immunohistologic test, a genetic test, a guaiac test, a test for fetal occult blood, a test for fecal blood, a test for fecal DNA, a test for a fecal cancer marker, a cancer test not based on a thrombospondin fragment or portion thereof, a receptor test, an estrogen receptor test, a disease test not based on a thrombospondin fragment or portion thereof, an endoscopy, an upper gastrointestinal endoscopy, a lower gastrointestinal endoscopy, a colonoscopy, a sigmoidoscopy, a gastroscopy, a laparoscopy, a laparatomy, a lymph node biopsy, a surgery, and a bronchoscopy.

49. A method of Paragraph 48 wherein the blood test is selected from the group consisting of a cancer antigen test, a cancer gene test, a cancer DNA test, a cancer mRNA test, a cancer RNA test, a cancer protein test, a cancer glycoprotein test, a cancer carbohydrate test, a cancer lipid test, a prostate specific antigen test, a test of carcinoembryonic antigen, a test of cancer antigen CA-125, a test of alpha-fetoprotein, a test of CA15-3, a test of CA19-9, a test of malignin, a test of anti-malignin antibody, a test of anti-secretory factor, a cancer antigen that contains a carbohydrate epitope, a cancer antigen that contains a protein or polypeptide epitope, a cancer antigen that contains a lipid epitope, a cancer antigen that contains a mixed epitope, CA 27.29, and episialin.

50. A method of Paragraph 21 or Paragraph 33 wherein the thrombospondin fragment or portion thereof comprise a detectable label.

51. A method of Paragraph 50 wherein the thrombospondin fragment or portion thereof being detected is a target and/or indicator fragment and wherein a known or unknown amount of an unlabeled or differently labeled fragment is also subjected to the method, said unlabeled or differently labeled fragment being a thrombospondin fragment or portion thereof.

52. A method of Paragraph 51 wherein the amount of the unlabeled or differently labeled fragment is known.

53. A method of Paragraph 51 wherein the amount of the unlabeled or differently labeled fragment is unknown.

54. A method of producing antibodies against a thrombospondin fragment of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Paragraph 6 or Paragraph 7 said method comprising administering said fragment, fragment portion or immunogenic portion thereof to an organism capable of producing antibodies.

55. A method of Paragraph 54 wherein polyclonal antibodies are produced.

56. A method of Paragraph 54 wherein monoclonal antibodies are produced.

57. An antibody produced by the method of Paragraph 54.

58. A cell line producing the monoclonal antibodies of paragraph 56.

59. The cell line of paragraph 58, wherein said cell line is selected from the group consisting of a hybridoma, a transfected cell line, and an infected cell.

60. A method of producing a peptide or non-peptide binding agent against a thrombospondin fragment of Paragraph 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, a fragment portion of Paragraph 6 or Paragraph 7, or epitope therein, said method comprising the steps of

1) a generating step (random, semi-random, directed, combinatorial, and/or other) to generate large numbers (>100) of diverse peptides and/or non-peptides;

2) a selection step to identify within this large number those peptides and/or non-peptides that bind to the thrombospondin fragment, fragment protion, and/or an epitope therein; and

3) optionally an improvement step for improving the peptide or non-peptide binding agent to achieve better affinity and/or specificity.

61. A method of Paragraph 60 wherein the binding agent is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a single-chain antibody, a non-antibody, a protein, a product of phage display, an aptamer, a DNA, an RNA, a modified DNA, a modified RNA, a carbohydrate, a glycosaminoglycan, a heparin, a glycoprotein, a proteoglycan, and combinations and derivatives thereof.

62. A method of Paragraph 60 wherein the optional step for improving the binding agent is selected from the group consisting of molecular evolution, mutation of crucial residues, making dimeric, trimeric or multimeric molecules, and incorporation of sequences from animals or humans exposed to or expressing antibodies against the fragment, portion, or epitope therein.

63. A method of Paragraph 60 wherein the initial set of diverse molecules is enriched by using sequences from animals or humans exposed to or expressing antibodies against the target.

64. A cell line capable of producing a binding agent produced by the method of paragraph 60.

65. The cell line of paragraph 64, wherein said cell line is selected from the group consisting of a hybridoma, a transfected cell line, and an infected cell.

66. A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, a thrombospondin fragment in a material taken or gathered from an organism, said kit comprising a thrombospondin fragment of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Paragraph 6 or Paragraph 7.

67. A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, one or more thrombospondin fragments in a material taken or gathered from an organism, said kit comprising a binding agent capable of binding said one or more of said fragments.

68. A kit of Paragraph 67 wherein said binding agent is a binding agent produced by the method of Paragraph 54 or Paragraph 60.

69 A kit of Paragraph 68 wherein said binding agent is a binding agent produced by the method of Paragraph 53 and/or the method of paragraph 54 and/or the method of 60 that binds to a thrombospondin fragment or epitope of paragraph 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and/or 13.

70. A kit of Paragraph 67 wherein said binding agent comprises a protein.

71. A kit of Paragraph 70 wherein said protein comprises a multi-chain antibody.

72. A kit of Paragraph 71 wherein said multi-chain antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

73. A kit of Paragraph 70 wherein said protein comprises a fragment of a multi-chain antibody.

74. A kit of Paragraph 70 wherein said protein comprises a single-chain antibody.

75. A kit of Paragraph 67 wherein said binding agent is derived from a phage display library.

76. A kit of Paragraph 70 wherein said protein is a non-antibody, said non-antibody being a protein that is neither a multi-chain antibody nor a single-chain antibody.

77. A kit of Paragraph 76 wherein said non-antibody is selected from the group consisting of a thrombospondin receptor, a thrombospondin binding protein, a thrombospondin receptor and/or binding protein that binds within a protease-resistant core region, a thrombospondin receptor and/or binding protein that binds a TSP fragment present in the plasma of a cancer patient, a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, an anti-secretory factor, an angiocidin, a 26S proteasome non-ATPase regulatory subunit 4, a CD36, a fragment thereof, a fragment thereof that binds to the respective target, and combinations, chimeras, and recombinant versions of said receptors and fragments.

78. A kit for the determination of the presence of, and/or the amount of, and/or the concentration of, one or more thrombospondin fragments in a material taken or gathered from an organism, said kit comprising a binding agent that will react with thrombospondin but not with the fragment or fragments of interest.

79. A kit of Paragraph 78 wherein said binding agent is a binding agent produced by the method of Paragraph 54 or Paragraph 60.

80. An method method comprising the following steps: (1) the method of Paragraph 52; (2) the method of Paragraph 53; and (3) a determination of the amount of the unlabeled or differently labeled fragment of paragraph 53 (the unknown) through comparison to the results obtained from the unlabeled or differently labeled fragment of paragraph 52 (the calibrator).

81. A kit of Paragraph 78 wherein said binding agent comprises a protein.

82. A kit of Paragraph 81 wherein said protein comprises a multi-chain antibody.

83. A kit of Paragraph 82 wherein said multi-chain antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

84. A kit of Paragraph 81 wherein said protein comprises a fragment of a multi-chain antibody.

85. A kit of Paragraph 81 wherein said protein comprises a single-chain antibody.

86. A kit of Paragraph 81 wherein said protein is derived from a phage display library.

87. A kit of Paragraph 81 wherein the protein is a non-antibody, a non-antibody being a protein that is neither an antibody nor a single-chain antibody.

88. A kit of Paragraph 87 wherein said non-antibody is selected from the group consisting of an integrin, an RGD receptor, an RFYVVMWK (SEQ ID NO:55) receptor, an RFYVVM (SEQ ID NO:56) receptor, an FYVVMWK (SEQ ID NO:57) receptor, an IRVVM (SEQ ID NO:58) receptor, a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, CD36, anti-secretory factor, angiocidin, 26S proteasome non-ATPase regulatory subunit 4, a fragment thereof that binds to the respective target, and combinations, chimeras, and recombinant versions of said receptors, integrins, and fragments.

89. A kit of Paragraph 67 wherein said binding agent comprises a non-protein.

90. A method of paragraphs 21, 33, 54, or 60, wherein said thrombospondin fragment or portion thereof has been derivatized.

91. A method of paragraph 90, wherein said derivatized fragment or portion thereof comprises a moiety selected from the group consisting of a label, a carrier, an albumin carrier, a keyhole limpet hemocyanin carrier, an epitope tag, an epitope, and an adjuvant.

92. A method of paragraph 90, wherein the derivatization is selected from the group consisting of addition of a detectable label, incorporation of a detectable label, conjugation to another molecule, synthesis of the fragment as part of a chimeric protein, linkage to a carrier molecule or particle, linkage to a carrier, linkage to a bead, linkage to a solid matrix, linkage to keyhole limpet hemocyanin, linkage to an albumin, linkage to an ovalbulin, linkage to a cross-linking agent, linkage to an epitope tag, and linkage to an epitope.

93. A kit for the determination of the presence of, and/or the amount of, thrombospondin

fragments in a material taken or gathered from an organism, said kit comprising an antibody that will react thrombospondin fragments of interest but not with thrombospondin.

94. A purified and/or synthetic thrombospondin fragment of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 or a fragment portion of Paragraph 6 or Paragraph 7, said fragment or portion thereof being derivatized.

95. A purified and/or synthetic fragment or portion thereof of Paragraph 94, wherein the derivatization is selected from the group consisting of addition of a detectable label, incorporation of a detectable label, conjugation to another molecule, synthesis of the fragment as part of a chimeric protein, linkage to a carrier molecule or particle, linkage to a carrier, linkage to a bead, linkage to a solid matrix, linkage to keyhole limpet hemocyanin, linkage to an albumin, linkage to an ovalbumin, linkage to a cross-linking agent, linkage to an epitope tag, and linkage to an epitope.

96. The fragment of paragraph 92 and/or Paragraph 95, wherein said label selected from the group consisting of a radioactive label, a fluorescent label, a chemical label, a colorometric label, an enzymatic label, a non-fluorescent label, a non-radioactive label, a biotin moiety, and an avidin moiety.

97. The fragment of Paragraph 92 and/or Paragraph 95, wherein said carrier is a moiety selected from the group consisting of a bead, a microsphere, a coded microsphere, a solid matrix, keyhole limpet hemocyanin, an albumin, an ovalbumin, linkage to a cross-linking agent, an epitope tag, and an epitope.

98. A method of Paragraph 21 said method comprising the step of binding a binding agent to the thrombospondin fragment or portion thereof.

99. A method of Paragraph 98 wherein said binding agent is a binding produced by the method ofParagraph 54 or 60.

100. A method of Paragraph 98 wherein said binding agent is a binding agent produced by the method of Paragraph 54 and/or Paragraph 60.

101. A method of Paragraph 100 wherein said binding agent comprises a protein and/or a polypeptide.

102. A method of Paragraph 101 wherein said protein comprises an antibody.

103. A method of Paragraph 102 wherein said antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

104. A method of Paragraph 101 wherein said protein and/or polypeptide comprises an antibody fragment.

105. A method of Paragraph 101 wherein said protein comprises a single chain antibody.

106. A method of Paragraph 101 wherein said protein and/or polypeptide is derived from a phage display library.

107. A method of Paragraph 101 wherein said protein is a non-antibody, said non-antibody being a protein that is neither a multi-chain antibody nor a single-chain antibody.

108. A method of Paragraph 107 wherein said non-antibody is selected from the group consisting of a thrombospondin receptor, a thrombospondin binding molecule, a thrombospondin receptor and/or binding molecule that binds within a protease-resistant core region, a thrombospondin receptor and/or binding molecule that binds a TSP fragment present in the plasma of a cancer patient, a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, an anti-secretory factor, a CD36, a fragment thereof, a fragment thereof that binds to the respective target, and combinations, chimeras, and recombinant versions of said receptors and fragments.

109. A method of Paragraph 98 wherein said binding agent is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a single-chain antibody, a non-antibody, a protein, a product of phage display, an anti-secretory factor, an aptamer, a DNA, an RNA, a modified DNA, a modified RNA, a carbohydrate, a glycosaminoglycan, a heparin, a glycoprotein, a proteoglycan, and combinations and derivatives thereof.

110. A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease; said fragment or fragments being a fragment of paragraphs 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12 and/or 13, and/or comprising an epitope therein.

111. A method of Paragraph 110 where the individual referred to therein is a first

individual and wherein the method further comprises the steps of:

(3) measuring a second individual's plasma level of the thrombospondin fragment, said second individual considered to not have neoplastic disease;

(4) utilizing the result of step (3) is the diagnosis of whether the first individual has a neoplastic disease.

112. A method of Paragraph 111, wherein the greater the extent to which the first individual's plasma thrombospondin fragment level exceeds the plasma thrombospondin level of the second individual, the more likely that the diagnosis will be that the first individual has a neoplastic disease and/or a neoplastic disease more advanced than that of the second persion.

113. A method of Paragraph 110 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment more than once, and utilizing the change in plasma level from an older to a more recent value to indicate appearance or progression or improvement wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by a decrease in said plasma level.

114. A method of Paragraph 113 wherein the plasma level of a thrombospondin fragment is assayed repeatedly.

115. A method of paragraph 114 wherein the repeated assays are performed at regular intervals, said intervals ranging from two weeks to 10 years.

116. A method of Paragraph 109, 110, 111, 112, 113, 114 or 115, wherein the neoplastic disease is selected from the group consisting of an adenoma, adenocarcinoma, carcinoma, lymphoma, leukemia, and sarcoma.

117. A method of Paragraph 109, 110, 111, 112, 113, 114 or 115, wherein the neoplastic disease is an internal cancer.

118. A method of Paragraph 109, 110, 111, 112, 113, 114 or 115,wherein the neoplastic disease is selected from the group consisting of a cancer of the respiratory system, a cancer of the circulatory system, a cancer of the musculoskeletal system, a cancer of a muscle, a cancer of a bone, a cancer of a joint, a cancer of a tendor or ligament, a cancer of the digestive system, a cancer of the liver or biliary system, a cancer of the pancreas, a cancer of the head, a cancer of the neck, a cancer of the endocrine system, a cancer of the reproductive system, a cancer of the

male reproductive system, a cancer of the female reproductive system, a cancer of the genitourinary system, a cancer of a kidney, a cancer of the urinary tract, a skin cancer, a cancer of other sensory organs, a cancer of the nervous system, a cancer of a lymphoid organ, a blood cancer, a cancer of a gland, a cancer of a mammary gland, a cancer of a prostate gland, a cancer of endometrial tissue, a cancer of mesodermal tissue, a cancer of ectodermal tissue, cancer of an endodermal tissue, a teratoma, a poorly-differentiated cancer, a well-differentiated cancer, and a moderately differentiated cancer.

119. A method of Paragraph 109, 110, 111, 112, 113, 114 or 115,wherein the neoplastic disease is selected from the group consisting of a cancer of solid tissue, a cancer of the blood or the lymphatic system, a solid cancer, a liquid cancer, a non-metastatic cancer, a premetastic cancer, a metastatic cancer, a cancer with vascular invasion, a skin cancer, a poorly differentiated cancer, a well-differentiated cancer and a moderately differentiated cancer.

120. A method of Paragraph 109, 110, 111, 112, 113, 114 or 115, wherein the measurement of a plasma thrombospondin fragment level comprises the use of a binding agent, said binding agent capable of binding said fragment.

121. A method of Paragraph 120 wherein said binding agent is a binding agent produced by the method of Paragraph 54 or 60.

122. A method of Paragraph 121 wherein said binding agent is a binding agent produced by a method of Paragraph 54 or Paragraph 60 that binds to a thrombospondin fragment or portion of paragraph 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and/or 13, or an epitope therein.

123. A method of Paragraph 110 wherein said binding agent comprises a protein and/or a polypeptide.

124. A method of Paragraph 123 wherein said protein comprises an antibody.

125. A method of Paragraph 124 wherein said antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

126. A method of Paragraph 123 wherein said protein comprises an antibody fragment.

127. A method of Paragraph 123 wherein said protein comprises a single chain antibody.

128. A method of Paragraph 120 wherein said binding agent comprises a non protein.

129. A method of Paragraph 123 wherein said protein and/or polypeptide is derived from

a phage display library.

130. A method of Paragraph 123 wherein said protein is a non-antibody, said non-antibody being a protein that is neither a multi-chain antibody nor a single-chain antibody.

131. A method of Paragraph 130 wherein said non-antibody is selected from the group consisting of a thrombospondin receptor, a thrombospondin binding protein, a thrombospondin receptor and/or binding protein that binds within a protease-resistant core region, a thrombospondin receptor and/or binding protein that binds a TSP fragment present in the plasma of a cancer patient, a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, an anti-secretory factor, an angiocidin, a 26S proteasome non-ATPase regulatory subunit 4, a CD36, a fragment thereof, a fragment thereof that binds to the respective target, and combinations, chimeras, and recombinant versions of said receptors and fragments.

132. A method of Paragraph 110 wherein said binding agent is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a single-chain antibody, a non-antibody, a protein, a product of phage display, an anti-secretory factor, an aptamer, a DNA, an RNA, a modified DNA, a modified RNA, a carbohydrate, a glycosaminoglycan, a heparin, a glycoprotein, a proteoglycan, and combinations and derivatives thereof.

133. A method of Paragraph 121 wherein the thrombospondin fragment is separated from thrombospondin before said fragment is bound to the binding agent.

134. A method of Paragraph 110 wherein said method comprises the use of a binding agent, comprising a binding agent capable of binding thrombospondin but not the thrombospondin fragment.

135. A method of Paragraph 134 wherein said binding agent is a binding agent produced by the method of Paragraph 54 or 60.

136. A method of Paragraph 134 wherein said binding agent is a binding agent produced by the method of Paragraph 54 or 60 that binds to a thrombospondin fragment or portion of Paragraph 6, Paragraph 7, Paragraph 9, Paragraph 11, and/or Paragraph 12 or an epitope therein.

137. A method of Paragraph 134 wherein said binding agent comprises a protein and/or polypeptide.

138. A method of Paragraph 137 wherein said protein comprises an antibody.

139. A method of Paragraph 138 wherein said antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

140. A method of Paragraph 137 wherein said protein comprises an antibody fragment.

141. A method of Paragraph 137 wherein said protein and/or polypeptide is derived from a phage display library.

142. A method of Paragraph 137 wherein said protein is a non-antibody, said non-antibody being a protein that is neither a multi-chain antibody nor a single-chain antibody.

143. A method of Paragraph 142 wherein said non-antibody is selected from the group consisting of an integrin, an RGD receptor, an RFYVVMWK (SEQ ID NO:55) receptor, an RFYVVM (SEQ ID NO:56) receptor, an FYVVMWK (SEQ ID NO:57) receptor, an IRVVM receptor (SEQ ID NO:58), a CSVTCG (SEQ ID NO:54) receptor, a CSVTCG (SEQ ID NO:54) binding molecule, CD36, anti-secretory factor, angiocidin, 26S proteasome non-ATPase regulatory subunit 4, a fragment thereof that binds to the respective target, and combinations, chimeras, and recombinant versions of said receptors, integrins, and fragments.

144. A method of Paragraph 134 wherein said binding agent selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a single-chain antibody, a non-antibody, a protein, a product of phage display, an anti-secretory factor, an aptamer, a DNA, an RNA, a modified DNA, a modified RNA, a carbohydrate, a glycosaminoglycan, a heparin, a glycoprotein, a proteoglycan, and combinations and derivatives thereof.

145. A method of producing antibodies against a thrombospondin fragment, said fragment at least 6 amino acyl residues in length, said method comprising administering said fragment to an organism capable of producing antibodies.

146. A monoclonal antibody produced by the method of Paragraph 145.

147. A cell line producing a monoclonal antibody of paragraph 146.

148. A polyclonal antibody preparation produced by the method of Paragraph 145.

149. A method of producing a binding agent against a thrombospondin fragment, said fragment at least 6 amino acyl residues in length, said method comprising binding a phage to said thrombospondin fragment.

150. A fragment or portion thereof of Paragraphs 6, 7, 8, 9, 10, 11, 12, or 13 further

modified to have a modification selected from the group consisting of glycosylation, β-hydroxylation, and addition of groups or moieties to aid conjugation and/or stability.

151. A fragment or portion thereof of paragraph 5 or 150, wherein said groups or moieties are selected from the group consisting of addition of a cysteine residue and addition of a terminal amino group.

152. A purified thrombospondin fragment, said fragment comprising at least 6 contiguous amino acyl residues from the thrombospondin sequence, wherein the amino acid sequence of the fragment is limited to one that is outside of a thrombospondin region defined in paragraph 6, and/or paragraph 7.

153. A method of Paragraph 54, 60, 145, and/or 149 wherein said fragment, fragment portion, or immunogenic portion is derivatized.

154. A purified and/or synthetic thrombospondin fragment of Paragraph 10, wherein the fragment comprises an amino acid sequence selected from the group consisting of TEENKE (SEQ ID NO: 1), CLQDSIRKVTEENKE (SEQ ID NO: 2), LQDSIRKVTEENKE (SEQ ID NO: 3), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEARE (SEQ ID NO: 5), EDTDLD (SEQ ID NO: 6), YAGNGIICGEDTDLD (SEQ ID NO: 7), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), RKVTEENKELANELRRP (SEQ ID NO: 9), CRKVTEENKELANELRRP (SEQ ID NO: 10), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), RKVTEENKE (SEQ ID NO: 13), and a portion at least 3 amino acyl residues in length (preferably at least 4 amino acyl residues in length, more preferably at least 6 amino acyl residues) of such an amino acid sequence.

155. A purified and/or synthetic thrombospondin fragment of Paragraph 10, wherein the fragment comprises an amino acid sequence selected from the group consisting of TERDDD (SEQ ID NO: 24), DFSGTFFINTERDDD (SEQ ID NO: 25), ERKDHS (SEQ ID NO: 26), TRGTLLALERKDHS (SEQ ID NO: 27), CTRGTLLALERKDHS (SEQ ID NO: 28), DDKFQD (SEQ ID NO: 29), ANLIPPVPDDKFQD (SEQ ID NO: 30), CANLIPPVPDDKFQD (SEQ ID NO: 31), DCEKME (SEQ ID NO: 32), EDRAQLYIDCEKMEN (SEQ ID NO: 33), CGTNRIPESGGDNSVFD (SEQ ID NO: 34), NRIPESGGDNSVFD (SEQ ID NO: 35), GWKDFTAYRWRLSHRPKTG (SEQ ID NO: 36), CGWKDFTAYRWRLSHRPKTG (SEQ ID

NO: 37), and a portion at least 3 amino acyl residues in length (preferably at least 4 amino acyl residues in length, more preferably at least 6 amino acyl residues) of such an amino acid sequence.

156. A purified and/or synthetic thrombospondin fragment of Paragraph 10, wherein the fragment comprises an amino acid sequence selected from the group consisting of DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23) and a portion at least 3 amino acyl residues in length (preferably at least 4 amino acyl residues in length, more preferably at least 6 amino acyl residues) of such an amino acid sequence.

157. A kit of paragraph 89 wherein the non-protein is an aptamer.

158. A purified and/or synthetic thrombospondin fragment or portion thereof, said fragment selected from the group comprising one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues K-412 and I-530, inclusive;

one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues I-530 and R-733, inclusive;

and one that starts between amino acyl residues I-165 and V-263, inclusive, and ends between amino acyl residues R-733 and Y-982, inclusive, said portion being at least 6 amino acyl acids in length.

159. A purified thrombospondin fragment, said fragment comprising at least 6 contiguous amino acyl residues from the thrombospondin sequence, wherein the amino acid sequence of the fragment is limited to one that is outside of a thrombospondin region defined in paragraph 6, paragraph 7, and/or paragraph 158.

160. The method of Paragraph 26 wherein in Step 1 the epitope comprises an amino acid sequence selected from the group consisting of a fragment of paragraph 6, a fragment of paragraph 7, a fragment of paragraph 9, a fragment of paragraph 11, a fragment of paragraph 12, TEENKE (SEQ ID NO: 1), CLQDSIRKVTEENKE (SEQ ID NO: 2), LQDSIRKVTEENKE

(SEQ ID NO: 3), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEARE (SEQ ID NO: 5), EDTDLD (SEQ ID NO: 6), YAGNGIICGEDTDLD (SEQ ID NO: 7), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), RKVTEENKELANELRRP (SEQ ID NO: 9), CRKVTEENKELANELRRP (SEQ ID NO: 10), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), RKVTEENKE (SEQ ID NO: 13), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion, at least 3 amino acyl residues in length of such an amino acid sequence.

161. The method of Paragraph 26 wherein in Step 2 the epitope comprises an amino acid sequence selected from the group consisting of a fragment of paragraph 8, TERDDD (SEQ ID NO: 24), DFSGTFFINTERDDD (SEQ ID NO: 25), ERKDHS (SEQ ID NO: 26), TRGTLLALERKDHS (SEQ ID NO: 27), (C)TRGTLLALERKDHS (SEQ ID NO: 28), DDKFQD (SEQ ID NO: 29), ANLIPPVPDDKFQD (SEQ ID NO: 30), (C)ANLIPPVPDDKFQD (SEQ ID NO: 31), DCEKME (SEQ ID NO: 32), EDRAQLYIDCEKMEN (SEQ ID NO: 33), CGTNRIPESGGDNSVFD (SEQ ID NO: 34), NRIPESGGDNSVFD (SEQ ID NO: 35), GWKDFTAYRWRLSHRPKTG (SEQ ID NO: 36), CGWKDFTAYRWRLSHRPKTG (SEQ ID NO: 37), DDDDNDKIPDDRDNC (SEQ ID NO: 14), DDDDNDKIPDDRDNC[NH2] (SEQ ID NO: 15), DDDDNDK (SEQ ID NO: 16), NLPNSGQEDYDKDG (SEQ ID NO: 17), CNLPNSGQEDYDKDG (SEQ ID NO: 18), EDYDKD (SEQ ID NO: 19), CPYNHNPDQADTDNNGEGD (SEQ ID NO: 20), YAGNGIICGEDTDLD (SEQ ID NO: 7), EDTDLD (SEQ ID NO: 6), CNSPSPQMNGKPCEGEAR (SEQ ID NO: 8), PQMNGKPCEGEARE (SEQ ID NO: 5), EGEARE (SEQ ID NO: 4), PQMNGKPCEGEAR (SEQ ID NO: 11), CEGEAR (SEQ ID NO: 12), CRLVPNPDQKDSDGD (SEQ ID NO: 21), DQKDSDGD (SEQ ID NO: 22), CPYVPNANQADHDKDGKGDA (SEQ ID NO: 23), and a portion, at least 3 amino acyl residues in length of such an amino acid sequence, provided that said peptide with a designated

SEQ ID NO. does not comprise an epitope used in step 1.

162. A method of Paragraph 137 wherein said protein comprises a single chain antibody.

163. A method of Paragraph 60 wherein the binding agent is an antibody induced by either thrombospondin, a modified form of thrombospondin, a fragment of thrombospondin, a fragment of a modified form of thrombospondin, or a modified fragment of thrombospondin.

164. A method of Paragraph 163 wherein a modified form of thrombospondin was generated by glycosylation, deglycosylation, β-hydroxylation, denaturation, renaturation, calcium depletion, calcium supplementation, alkylation, reduction, conjugation, and/or addition of groups or moieties to aid conjugation, stability, and/or immunogenicity of thrombospondin; and wherein a modified fragment of thrombospondin was generated by glycosylation, deglycosylation, β-hydroxylation, alkylation, reduction, conjugation, and/or addition of groups or moieties to aid conjugation, stability, and/or immunogenicity of said fragment. --